isolating a population of nucleic acids encoding human antibody chains from lymphatic cells of the transgenic mouse;

forming a library of display packages displaying the antibody chains, wherein a library member comprises a nucleic acid encoding an antibody chain, and the antibody chain is displayed from the package, wherein the library comprises at least 100 members at least 50% of which comprise nucleic acids encoding human antibody chains showing at least 10^9 M^{-1} affinity for the same target and no library member constitutes more than 50% of the library.

Q1

Amended
4. ^ The method of claim1, wherein the display package comprises a phagemid vector.

Q2

Amended
5. ^ The method of claim 1, wherein the nucleic acids encode variable regions of the antibody chains and the display package comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region.

Amended
9. ^ The method of claim 1, further comprising contacting libraries members with a target, whereby library members displaying an antibody chain and binding partner (if present) with specific affinity for the target bind to the target, and separating display packages displaying antibody chains bound to the target to produce a subpopulation of display packages.

Q3

Amended
10. ^ The method of claim 9, further comprising immunizing the transgenic mouse with an antigen.

Q4

Amended
15. ^ The method of claim 14, further comprising subcloning en masse nucleic acids encoding antibody chains from the further subpopulation of library

Q4

members into multiple copies of an expression vector to form modified expression vectors.

Amended

17. A method of producing a human Fab phage display library, comprising:

providing a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies;

isolating populations of nucleic acids respectively encoding human antibody heavy chains and human antibody light chains from lymphatic cells of the transgenic mouse;

Q5

cloning the populations into multiple copies of a phage display vector to produce a display library, wherein a library member comprises a phage capable of displaying from its outersurface a fusion protein comprising a phage coat protein, a human antibody light chain or human antibody heavy chain, wherein in at least some members, the human antibody heavy or light chain is complexed with a partner human antibody heavy or light chain, the complex forming a Fab fragment to be screened, wherein the library comprises at least 100 members at least 50% of which comprise nucleic acids encoding Fab fragments showing at least 10^9 M^{-1} affinity for the same target and no library member constitutes more than 50% of the library.

Amended

23. The method of claim 17, further comprising contacting libraries members from the display library with a target, whereby library members displaying a Fab fragment with specific affinity for the target bind to the target, and separating phage displaying Fab fragments bound to the target to produce a further subpopulation of phage.

Q6

Amended

25. The method of claim 17, further comprising immunizing the transgenic mouse with an antigen.

Q7

35. Amended A library of at least 100 different nucleic acid segments encoding human antibody chains, wherein at least 50% of segments in the library encode human antibody chains showing at least 10^9 M^{-1} affinity for the same human target and no library member constitutes more than 50% of the library.

Q8

36. Amended The library of claim 35, wherein the library comprises at least 100 pairs of different nucleic acid segments, the members of a pair respectively encoding heavy and light human antibody chains, wherein at least 50% of the pairs encode heavy and light human antibody chains that form complexes showing specific affinity for the same target, and no pair of nucleic acid segments constitutes more than 50% of the library.

42. Amended A library of at least 100 different nucleic segments encoding human antibody chains, wherein at least 90% of segments in the library encode human antibody chains having an affinity of at least 10^9 M^{-1} for the same human target and no library member constitutes more than 50% of the library, and the library is free of segments encoding human lambda light chains.

Q9

43. Amended A library of at least 1000 different nucleic segments encoding human antibody chains, wherein at least 90% of segments in the library encode human antibody chains having an affinity of at least 10^9 M^{-1} for the same human target and no library member constitutes more than 50% of the library, wherein each segment comprises subsequence(s) from a human VH or a human VL gene, or both and no more than 40 human VH genes and no more than 40 human VL genes are represented in the library.

44. Amended A library of at least 100 types of human antibodies, wherein at least 50% of the types of human antibodies in the library have an affinity of at least 10^{10}

a9

M^{-1} for the same human target and no type of library member constitutes more than 25% of the library.

Please add the following new claims:

a10

46. The method of claim 1, wherein the transgenic mouse comprises less than the full complement of human immunoglobulin genes present in a human being, and the method further comprises amplifying the population of nucleic acids using a set of primers selected based on which human immunoglobulin genes from the full complement of human immunoglobulin genes are present in the genome of the transgenic mouse.

REMARKS

Support for the recital of a human target in claim 35 and other claims is provided at e.g., p. 8, line 11. Support for new claim 46 is provided by e.g., p. 11, lines 14-15 (less than full complement of human immunoglobulin genes) and p. 42, lines 7-16 indicating that different sets of primers are used depending on the transgene present a transgenic mouse. For example, cDNA from transgenic mice having the HCo7 transgene is amplified using one set of primers, cDNA from transgenic mice having the HCo12 transgene is amplified using a second set of primers, and cDNA from transgenic mice having both the HCo7 and HCo12 transgenes is amplified using both sets of primers. Claim amendments should not be viewed as an acquiescence in any ground of rejection.

Claim Objections

Claims 17 and 35 have been amended as suggested.

Sequence compliance

A sequence listing is attached.